Disease Questionnaire (IBDQ)]. Over the years a standardized document was developed to help the authors to clarify the concepts and intent of each item of their questionnaire(s). This document and examples will be presented. **CONCLUSIONS:** This review demonstrates the lack of a formal, written concept lists for PRO questionnaires developed before the publication of the FDA guidance and the need to develop standardized documents. Involvement of the developer(s) is crucial at this step.

Research on Methods – Statistical Methods

PRM36
NONPARAMETRIC ESTIMATION OF INCREMENTAL COST EFFECTIVENESS RATIO ACCOUNTING FOR SKEWNESS

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OBJECTIVES: Typically, mean costs and mean measures of effectiveness are used in the estimation of the incremental cost effectiveness ratio (ICER). Cost and effectiveness distributions, however, are often skewed. The goal of this work is to use a nonparametric generalization of location to obtain a location region in the cost effectiveness plane. The region accounts for uncertainty and all points in the region are appropriate estimates of the ICER that account for skewness in the marginal distributions. **METHODS:** First, analogous to Mann-Whitney, all pairwise cost and effectiveness treatment differences are computed. Using univariate methods, an estimate of a location rectangle is obtained as the Cartesian product of marginal location intervals, intervals that account for skewness. By considering the intersection of such rectangles over all orthogonal transformations, a closed convex region is obtained. This method will then be applied to simulated bivariate cost effectiveness data using both symmetric and skewed distributions. Kolmogorov-Smirnov provides simultaneous confidence bands for each univariate rectangle. Any point of this region is an estimate of the ICER; all such points satisfy basic axioms of bivariate location. This approach will also be used to construct a generalization of the cost effectiveness acceptability curve with uncertainty incorporated. A test for marginal skewness can precede the construction of the location region. **RESULTS:** By comparing the location region with the usual bootstrap estimates for the ICER, it was found that the location region approach produced confidence intervals that were considerably larger for both skewed and symmetric distributions of costs and effectiveness. **CONCLUSIONS:** This work provides estimates of the ICER that appropriately accounting for skewness. In such cases, the mean is not the best measure of location. In spite of the used of the nonparametric bootstrap to obtain confidence intervals, skewness introduces an extra element of variability that should be accounted for.

PRM37
THE DISCRETE MODELLING OF INTERVENTIONS WITH CONTINUOUSLY VARYING COSTS AND EFFECTS: IMPLICATIONS FOR ICERS, CEACS AND EVPI

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OBJECTIVES: To show how the discrete modelling of continuously varying dose-response relationships in cost-effective analysis (CEA) influences incremental cost-effectiveness ratios (ICERs), cost-effectiveness acceptability curves (CEACs) and the expected value of perfect information (EVPI). In particular, to show that each of these metrics is contingent on the discrete comparisons chosen within a CEA. **METHODS:** The cost-effectiveness of a hypothetical intervention with a continuous dose-response relationship is simulated. The cost-effectiveness of a small number of possible dose levels is simulated first. The analysis is then repeated a number of times, progressively increasing the number of possible doses and resulting combinations of costs and effects. For each run of the analysis ICERs are calculated for each dose level, a probabilistic sensitivity analysis is simulated, and CEACs and the EVPI are plotted. **RESULTS:** As the number of potential cost and effect combinations increases, the ICERs for each dose level increase, the CEACs fall towards zero and the EVPI both rises and changes from having sharp inflection points to being a smooth, downward-sloping curve. **CONCLUSIONS:** Many interventions demonstrate dose-response relationships, most of which are in principle continuous, even if doses are typically varied discretely. The continuously increasing intensity of interventions means the number of possible alternatives is infinite. The general conclusion from the analysis is that each of the metrics presented here are contingent on the discrete comparisons chosen within the analysis. The significance of this finding for CEACs depends on their interpretation, which varies in the literature. The significance for EVPI is that while it has previously been recognised that excluding relevant comparators can reduce the EVPI, including all theoretically relevant alternatives may be impossible. Further work may be required to understand this constraint on measuring the upper bound of the value of further research.

PRM38
THE EXTENSION OF THE COST-EFFECTIVENESS ACCEPTABILITY CURVE: HOW TO MAKE IT MORE INFORMATIVE?

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OBJECTIVES: To develop new schemes which can make the cost-effectiveness acceptability curve (CEAC) augmented to be more informative regarding the types of acceptance and statistical inference. **METHODS:** Theoretical approaches have been undertaken to address two questions: how the area under the curve (AUC) can be zoned by the types of acceptance, and how the accepted dataset of incremental cost-effectiveness ratios (ICERs), which are generated by computer runs, can be statistically associated with a standard threshold of ICER. **RESULTS:** The AUC of a typical sigmoid-shaped CEAC was divided into three zones, each of which represents the proportion, $p_i = n_i / n(\lambda_0)$, where n_i is the number of plots on the cost-effectiveness plain belonging to the quadrant i (i=1:South-East, 2:North-East and 3:South-West), and $n(\lambda_0)$ is the total number of plots (i.e., $n(\lambda_0)=n_1+n_2+n_3$) accepted for the threshold, λ_0, of ICER. A solution for the second question was "a new CEAC of the mean (MCEAC)", which can be constructed by plotting a pair of m_0 and p_0 instead of a pair of λ_0 and p_0, where λ_0: the threshold of ICER for acceptance, p_0: the probability of acceptance for the threshold λ_0, and m_0: the mean ICER of all the plots accepted for the threshold λ_0. Also, statistical validity of the MCEAC was inferred by the confidence interval of the mean m_0 using t-test. Furthermore, the series of confidence intervals defined for one threshold λ_0 corresponding to different size of computer runs were summarized as a diagram for showing the progression of the confidence intervals, which looks similar to the forest plot in meta-analysis. All those schemes were graphically illustrated based on examples. **CONCLUSIONS:** Visualizing the component types of acceptance in the AUC, drawing the MCEAC, and the progression diagram of confidence intervals will provide us with more useful information on cost-effectiveness decisions.

Research on Methods – Study Design

PRM39
LITERATURE REVIEW OF RANDOMIZED, CONTROLLED STUDIES OF THE IMPACT OF PHARMACISTS' INTERVENTIONS TO IMPROVE PATIENT OUTCOMES

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OBJECTIVES: The objective was to summarize the impact of pharmacists' interventions on patient outcomes as reported in studies utilizing a randomized controlled trial (RCT) design. **METHODS:** A comprehensive literature search was conducted utilizing PubMed and International Pharmaceutical Abstracts for the years 1979-2009. Studies were included if they evaluated pharmacist-provided interventions, utilized RCT designs with control groups, and were conducted in the United States. Studies were summarized by 1) publication year; 2) study setting; 3) disease/health condition; and 4) type of intervention provided and whether performed by a pharmacist alone or a pharmacist with other health care professionals, 5) primary outcome variables and 6) study findings. Patient outcome results were categorized as 'positive', if they found a statistically significant improvement in the patient outcomes when compared to the control group, or 'no difference' if no significant difference was found. **RESULTS:** Of the 552 citations reviewed, 100 studies met the inclusion criteria. The numbers of pharmacists' intervention studies conducted using RCT designs increased from 1979 to 2009, with 64% conducted after 2000. The majority of the studies were conducted in clinic setting (65%) followed by community pharmacies (19%), hospitals (12%), home-care (2%), and multiple settings (2%). Chronic conditions were studied in 56% of the studies. Studies of interventions delivered by pharmacists alone comprised 64%, while 36% involved pharmacists working with other health care providers. Overall, 'positive' patient outcomes were demonstrated in 73% of the studies. When interventions were delivered by pharmacists working with other health care providers, however, 97.2% had positive outcomes. **CONCLUSIONS:** 'Positive' patient outcomes were demonstrated in the majority of the studies, supporting increased pharmacists' roles in the health care system to improve patient outcomes. When working alongside other health care providers, the positive impact was most likely.

Research on Methods – Conceptual Papers

PRM40
ISSUES CONCERNING THE TRANSLATION OF THE WORD 'HASSLED' IN THE MORISKY MEDICATION ADHERENCE SCALE (MMAS-8)

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OBJECTIVES: The word 'hassle' is commonly used in PRO measures including the Morisky Medication Adherence Scale (MMAS-8). The translation of the word 'hassle' is used as an example of how creation of a concept elaboration and a full translation and linguistic validation process can result in a translation that is conceptually equivalent to the source text and to aid in the future translation of ambiguous words. **METHODS:** The MMAS-8 was translated into 29 languages using the standard methodology of two forward translations, reconciliation, two back translations, back-translation review, developer review and proofreading. Examples of translation issues of the word 'hassled' in the following statement were assessed: Do you ever feel hassled about sticking to your anti-rejection treatment plan? **RESULTS:** A 'hassle' is defined in the Oxford English Dictionary as an 'irritating inconvenience'. In the above question, this word encompasses several concepts – bothered, troubled, disturbed – which were provided to translators in a concept elaboration document. The translation process resulted in the following: The initial French translation was back-translated as bothered/annoyed. Alternatives back-translating as 'preoccupied' and 'inconvenient' were suggested but rejected. The developer piloted the final suggestion, **debordé** (overwhelmed), with French-speaking students, who agreed that this was the best translation in this context. For other languages, 'hassled' was translated variously as: a nuisance, cumbersome, difficult, bothersome, troubling, tiresome, irksome, burdensome and complicated. These were queried with translator and the developer to confirm concep-

tual equivalence to 'hassled'. **CONCLUSIONS:** Though not always possible to translate an English word exactly into the target language, a full translation and linguistic validation process, including creation of a concept elaboration document followed by an in-depth discussion at back-translation review stage, enables a conceptually equivalent translation to be found. The concept elaboration document should, where possible, be created in conjunction with the instrument developer.

PRM41

IS IT TIME TO ELIMINATE THE ICER? USING NET BENEFITS TO REPORT THE RESULTS OF DETERMINISTIC COST-EFFECTIVENESS ANALYSES

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BACKGROUND: Incremental cost-effectiveness ratios (ICERs) are used to report the results of cost-effectiveness (CE) analyses and represent the cost per unit of effectiveness of a more costly and more effective option. However, numerous conceptual and practical problems limit the usefulness of ICERs for decision making. These problems include, but are not limited to, negative ICERs, one-way sensitivity analyses, complexity of multiple comparator analyses, and statistical limitations with ratios. The net benefits approach was developed to address the statistical limitations of ICERs and is now an accepted methodology used in probabilistic sensitivity analysis to estimate CE confidence intervals and plot acceptability curves. However, despite the remaining challenges and limitations the use of ICERs persists, raising the question: Is it time to eliminate the use of ICERs in the reporting of CE analyses? **METHODS:** We propose expanding the net benefit method to present deterministic CE analysis results using a net monetary benefit (NMB) chart or table. A NMB chart is plotted with the x-axis representing the WTP threshold and the y-axis representing the NMB. The NMB of each option is a line with the intercept representing the cost and the slope representing the effectiveness across a specified range of WTP values. The line with the greatest NMB at a given WTP represents the most cost-effective option at that WTP. The vertical distance between two lines represents the incremental NMB. Dominance, extended dominance, and the frontier are captured graphically and intuitively. Multiple comparator analyses are simplified and one-way sensitivity analyses are enhanced due to the elimination of negative ICERs. **CONCLUSIONS:** A net benefits approach provides a more intuitive, informative, and useful method to present CE results than the use of ICERs. Moreover, it has the benefit of facilitating a uniform and consistent approach to presenting the results of deterministic and probabilistic CE analyses.

PRM42

VISUALLY EVALUATING THE MEASUREMENT COMPARABILITY BETWEEN PAPER-BASED AND ALTERNATE VERSIONS OF ADMINISTRATION OF THE LUNG FUNCTION QUESTIONNAIRE

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In randomized crossover designs, intraclass correlation coefficients (ICCs) are often used to assess the concordance between scores on different administration versions of patient-reported outcome (PRO) measures. An ICC and its associated criterion for "adequate" concordance enable analysts to simplify information and provide researchers with a quick and easy way to interpret analysis output. This strength of the ICC—its simplicity—may also be a weakness. Analysts may overlook important information (e.g., biases, outliers) when ICCs are used as the primary method for assessing concordance. One way to avoid overlooking important information is to include the evaluation of Bland-Altman plots when assessing concordance. Bland-Altman plots allow one to visually determine whether two measures produce similar scores, therefore, supplementing the concordance information gained from the ICC evaluation. ICCs and Bland-Altman plots complement each other's strengths. ICCs provide an efficient and concise estimate to determine the comparability of versions, while Bland-Altman plots provide a greater level of detail that incorporates a broader view of the analyzed distributions. The use of the two methods together provides a more holistic view of concordance. We present Bland-Altman plots and corresponding ICCs under a randomized crossover-design, using the Lung Function Questionnaire, a PRO instrument originally designed to be administered via paper, and later via three alternate administration versions (Web, interactive voice response system, and interview). We provide examples to illustrate instances in which ICCs and Bland-Altman plots agree and disagree. GSK study number: ADC001HO.

PRM43

BIOSIMILARS: DEMONSTRATING SIMILARITY THROUGH EVIDENCE

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OBJECTIVES: The differences in the active substance of biosimilars compared to their originator reference product can cause risks that are unique to biologics, mainly: immunogenicity, long-term safety risks, and lack of efficacy. These risks are unknown at the launch of a biosimilar and can lead to unexpected costs for payers. The aim of this abstract is to describe a methodology for evaluating the unknown risks of biosimilars. **METHODS:** A structured literature review revealed that for many biologics, post-marketing observational studies have been set up to identify long-term safety and efficacy outcomes. These studies are a useful source of information to quantify the unknown risks of biosimilars and define methods of minimizing those risks. The information required is product- and population-specific. This information first includes potential safety issues such as immunogenicity (all biologics), serious infections and autoimmune disorders (anti-TNFs, interferons), and increased mortality and cardiovascular events (epoetin). Second, information is available on long-term benefits such as clinical outcomes that improve overall survival (e.g. reduced recurrence of malignancies through interferon use and reduced cardiovascular events through insulin use), reduction in healthcare resource utilization (epoetin, somatropin), and proportion of long-term responders (figrastim, anti-TNF, somatropin). Finally, observational data can be used to optimize treatment regimens to achieve maximum treatment benefit (epoetin, insulin, somatropin). All these data can be used in an economic evaluation where the unknown risks for biosimilars are quantified through worst- and best-case scenarios. **CONCLUSIONS:** Often, payers are attracted to biosimilars that have the lowest acquisition costs. However, the risks of unknown information for these biosimilars should be valued against the lower price of these drugs. Observational data for the originator biologic product can be leveraged to quantify these risks. This can help determine for which drugs and for which populations the unknown risks outweigh the reduction in acquisition costs.

PRM44

OPTIMUM METHODS FOR PRO TRANSLATION AND LINGUISTIC VALIDATION METHODOLOGY: ONE BACK TRANSLATION OR TWO?

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OBJECTIVES: The translation of PRO measures requires a rigorous procedure, including dual forward translations, reconciliation, back translation and review, and debriefing interviews. The relevance of including blinded back translations has been widely discussed; however, there has been little discussion around back translation methods. This research aims to gauge the importance of having two back translations versus only one. **METHODS:** Past translation and linguistic validation projects employing the procedures outlined above were reviewed to compare the methodology of using one back translation versus two. **RESULTS:** In the dual-back projects, numerous instances were found in which only one back translator detected an issue. For example: 1. Simple mistranslations can be revealed by one translator but not another; e.g. 'activities at home' was back translated verbatim by one back translator but as 'household activities' by another, revealing that the translated term was too narrow and related only to chores; 2. Similarly, contextual mistranslations may become apparent in dual back translations. In one ePRO script, 'enter training module' meant to click through to the next page. One back translator wrote 'enter', while 'insert' in the second translation highlighted that the wrong term had been used in this context; 3. Dual translations are also useful for elucidating nuances in meaning. In Danish, the phrase 'bad tempered' became 'lose my temper' in one back translation, allowing the lead translator to alter the ambiguous translation; 4. Dual meanings in the target language may also be highlighted, for example in Gujarati 'hospitalisations' was correctly back translated by one translator, but the other translated it as 'clinic', showing an ambiguity in the translation. **CONCLUSIONS:** The high proportion of issues highlighted by only one back translator, show the importance of using two blinded back translators in the translation of PRO measures.

PRM45

PILOT TESTING TRANSLATIONS OF PRO MEASURES WITH SENSITIVE POPULATIONS

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The ISPOR Principles of Good Practice paper on the translation of patient-reported outcome (PRO) measures includes cognitive debriefing as a key step in the translation process. Cognitive debriefing refers to the process of asking patients to describe to an interviewer what each question/instruction means to them in their own words. This allows experienced project managers to then determine whether the patient has correctly understood the conceptual meaning of the question/instruction and therefore, by implication, whether the translation is accurate. Despite the FDA guidelines emphasising the importance of assessing the content validity of PRO translations, cognitive debriefing is not always feasible or ethically acceptable with certain patient groups. These groups include children, severely ill patients and patients with mental health problems, for whom prolonged interviews could cause distress. In these circumstances, alternative methodologies should be employed to establish whether the wording is suitable for the given population. Evidence from working with such patients indicates that clinician reviews, caregiver reviews and assessments of language complexity and suitability are all useful alternative methods for establishing the acceptability of PRO translations for particular patient populations. Two examples include pilot testing mental health measures with clinicians as a substitute for patients experiencing acute symptoms and pilot testing paediatric measures with health practitioners and teachers working with children from the target age group. Cognitive debriefing is a useful tool in the translation and linguistic validation of PRO measures but a more flexible approach is required to ensure that certain patients are not unduly distressed and burdened by the process.

PRM46

R . . . YOU AWARE HOW USEFUL IT IS? THE VALUE OF CORRELATION COEFFICIENTS IN META-ANALYSIS

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Meta-analysis involves pooling effect sizes to combine results from studies attempting to answer similar research questions. Typically, a common metric is used to estimate associations between independent and dependent variables in pooled studies. Nonetheless, studies vary considerably in their measurement of effect sizes as well as the nature of studied variables. The calculation of an effect size *r* allows the pooling of results that are reported in a variety of forms. In the presence